Whipple's disease

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INTRODUCTION

In 1907, George H Whipple described a 36-year-old clinician with "gradual loss of weight and strength, stools consisting chiefly of neutral fat and fatty acids, indefinite abdominal signs, and a peculiar multiple arthritis" [1]. The patient died of this progressive illness; Whipple called it intestinal lipodystrophy since he observed accumulation of "large masses of neutral fats and fatty acids in the lymph spaces." It was renamed Whipple's disease in 1949 upon description of the sine qua non of this disorder, accumulation of macrophages in the lamina propria with intensely periodic acid-Schiff (PAS)-positive intracellular material [2]. An infectious etiology was suspected as early as Whipple's initial report; however, successful treatment with antibiotics was not reported until 1952 [3].

Scientific understanding of the histology, immunology, and treatment of Whipple's disease has improved since the initial description, and the etiologic agent was identified in 1991. The cause is now known to be *Tropheryma whipplei* (from the Greek "trophe," nourishment, and "eryma," barrier, in reference to the nutrient malabsorption characteristic of the disease), a discovery made upon application of a new technique for identifying microbes based upon the DNA sequence encoding their 16S ribosomal RNA. *T. whipplei* is closely related to many other soil-borne actinomycetes [4,5].

This topic discusses the clinical manifestations, diagnosis, and treatment of Whipple's disease. Discussion of the approach to chronic diarrhea and the evaluation of polyarticular pain in adults

is found elsewhere. (See "Approach to the adult with chronic diarrhea in resource-abundant settings" and "Evaluation of the adult with polyarticular pain".)

MICROBIOLOGY

Whipple's disease is caused by *T. whipplei*, a gram-positive bacillus related to Actinomycetes. Whipple suspected an infectious agent in 1907 when he noted the numerous "rod-shaped organisms" within the submucosa and macrophages of the index patient. Careful light and electron microscopy by numerous investigators between 1960 and 1992 subsequently identified a gram-positive, non-acid-fast, periodic acid-Schiff (PAS)-positive bacillus with a characteristic trilamellar plasma membrane surrounded by a cell wall.

Application of polymerase chain reaction (PCR) allowed identification of a unique bacterial 16S ribosomal RNA in the intestinal and lymphatic tissue of 5 patients with Whipple's disease that was absent in 10 control patients [5]. Culture of the organism is extremely difficult. This had not been achieved until a 1997 report in which *T. whipplei* was propagated in cell culture; deactivation of peripheral blood monocytes with interleukin-4 was required for intracellular growth to occur [6]. Unfortunately, this culture technique could not be reproduced [7].

Subsequently, a group from France was able to grow the organism in a human fibroblast cell line (HEL), subculture it successfully, demonstrate characteristic morphology by electron microscopy, and raise antibodies in mice that reacted with patient samples by immunofluorescence [8]. The specimen was obtained from the heart valve of a patient with endocarditis caused by Whipple's disease. The organism has also been isolated from duodenal mucosa and CSF [9,10]. It appears to grow slowly (with a generation time estimated at four days in the report of successful cultivation from the CSF [10]).

T. whipplei has also been cultured from the feces of a patient with Whipple's disease [11]. The investigators decontaminated the specimen with glutaraldehyde, to which the organism is uniquely resistant, in order to isolate the bacterium and cultivate it in a specific axenic medium. The strain, which has been repeatedly subcultured, was confirmed by genotyping to be the same as that found in the duodenal biopsy specimen from the patient. The authors speculate that the organism may be transmitted by fecal-oral contamination; the fact that it is resistant to glutaraldehyde is problematic as this substance is widely used for disinfection.

A cell-free culture system for *T. whipplei* using defined culture medium was developed, based on the genome analysis of metabolic pathways [12]. However, it is unclear if the bacteria grown in

cell-free culture medium are biologically and immunologically identical with those grown in cell culture.

EPIDEMIOLOGY

T. whipplei, the agent of Whipple's disease, is ubiquitous in the environment. The bacterium has been detected in sewage and is more prevalent in the fecal samples of sewage workers (12 to 26 percent) than the general population [13,14]. There may also be variable geographic distribution of the organism, as the prevalence of asymptomatic carriage varies by region [15-20].

Not all individuals who encounter the agent develop Whipple's disease. Classic, late-onset Whipple's disease is extremely rare. Between 1907 and 1987, there were 696 reported cases; the annual incidence since 1980 has been approximately 30 cases per year. One study suggests that the disorder has a predilection for White males of European ancestry, suggesting an underlying genetic predisposition that leads to colonization of *T. whipplei* throughout the intestinal tract, lymphoreticular system, and central nervous system upon exposure to soil microbes [21]. A review of 664 patients found that [22]:

- 86 percent were male, with a mean age at diagnosis of 49 years
- 35 percent were farmers, and 66 percent had occupational exposure to soil or animals

However, in a subsequent database study from the United States, in which 350 of over 35 million individuals had a coded diagnosis of Whipple's disease, the diagnosis was similarly prevalent among males and females and was more common among individuals over 65 years of age; it was also more common among White and non-Hispanic individuals [23].

There has been no consistent familial clustering other than rare reports. An association between Whipple's disease and HLA-B27 has been postulated but not confirmed [24,25]. An association between HLA alleles DRB1*13 and DQB1*06 and Whipple's disease has been shown in a cohort of 122 European patients [26].

PATHOGENESIS

The pathogenesis of Whipple's disease remains obscure. However, the sequencing of the genome of the organism [27] is likely to facilitate studies of pathogenesis. Invasion or uptake of the bacillus is widespread throughout the body, including the intestinal epithelium, macrophages, capillary and lymphatic endothelium, colon, liver, brain, heart, lung, synovium,

kidney, bone marrow, and skin. All of these sites show a remarkable lack of inflammatory response to the bacillus. In addition, the organism exerts no visible cytotoxic effects upon host cells, thereby allowing massive accumulation of *T. whipplei* at sites of infection.

The clinical manifestations of infection do not seem to be determined by pathogen specific factors; no correlation has been observed between variable genomic sequences of *T. whipplei* and clinical manifestations [28].

Host factors — The lack of immunologic response has led many investigators to implicate host immune deficiency as a predisposition to the disease. This hypothesis is supported by the following observations:

- Patients with Whipple's disease have consistently shown decreased reactivity to mitogens such as phytohemagglutinin (PHA) and concanavalin-A, but have normal levels of immunoglobulins, suggesting a specific defect in cell-mediated immunity [29].
- Populations of intestinal and peripheral T-cells in acute Whipple's disease are characterized by a low CD4/CD8 T-cell ratio, increased activation, and a shift towards mature T-cell subpopulations [29-31].
- Whipple's disease is associated with a low functional activity of type 1 T-helper cells (Th1) in the periphery and the intestinal mucosa. In contrast, functional Th2 responses, characterized by enhanced expression of interleukin-4 (IL-4), are increased [32].
- Treatment with recombinant interferon gamma (IFN gamma) together with antimicrobials has led to clearance of infection in a chronically relapsing patient [33].
- Antigen presentation by the MHC class II apparatus is absent or diminished on the intestinal epithelial cells of patients with active Whipple's disease [34]. These findings normalize with treatment, suggesting a secondary effect such as immune downregulation by the bacteria [34].
- There may be a defect in host mononuclear cells, manifested by persistent deficiency in the expression of complement receptor type 3 (CD11b) [29], persistently diminished ability to degrade intracellular organisms [35], and impaired production of interleukin-12, an important stimulator of T-cell function [29,31].
- Patients with Whipple's disease have impaired immune function of monocytes and macrophages. In such patients, a reduced number of inducible nitrite synthetase-positive macrophages has been observed. Incubation of peripheral monocytes from Whipple's disease patients results in the expression of CD163, a marker of alternatively activated

monocytes. This may explain the reduced oxidative burst upon incubation with *T. whipplei* observed in Whipple's disease patients but not in controls [36].

- The organism is detectable in the saliva in up to 35 percent of healthy individuals and in the dental plaque and feces of healthy hosts [15-18], although it is rarely found in intestinal mucosa in the absence of histopathologic evidence of Whipple's disease [37].

- IgG antibodies against *T. whipplei* are detectable in about 70 percent of healthy individuals [8], in accordance with the theory of frequent exposure to the potential pathogen.

- Increased numbers of regulatory T cells can be detected within the duodenal mucosa in untreated classic Whipple's disease, in which huge numbers of *T. whipplei*-infected macrophages are present [38]. Regulatory T cells might contribute to the persistence and dissemination of *T. whipplei* in classic Whipple's disease, but prevent mucosal barrier defect by reducing local inflammation.

- Dendritic cells from patients with classic Whipple's disease demonstrate dysfunctional IL-12 production [39]. This can negatively impact priming of *T. whipplei*-specific T cells, and immature dendritic cells that carry *T. whipplei* might contribute to the systemic spread of the organism.

- Analysis of the transcriptional profile of intestinal macrophages in a patient with therapy refractory intestinal Whipple's disease revealed up-regulation of genes encoding CCL18, IL-10, cathepsin, MHC class II, scavenger receptor, CD14, and IL-1. All these up-regulated genes have been associated with the M2/alternatively activated phenotype of macrophages [40,41].

- In patients with Whipple's disease, *T. whipplei* replication was higher than in healthy subjects and was related to high levels of circulating IL-16 [42]. Both events were corrected in patients who successfully responded to antibiotic treatment.

- Using *T. whipplei* lysates for specific stimulation of peripheral blood and mucosal lymphocytes from healthy controls and from patients with Whipple's disease lead to intracellular IFN gamma production only in healthy controls but not in Whipple's disease patients [43]. The reaction of lymphocytes on stimulation with antigens from other pathogens was equivalent in the two groups. These data indicate a specific immunological defect in Whipple's disease patients.

Taken together, these observations suggest underlying host immune deficiency and possibly secondary immune downregulation induced by the bacterium. This likely results in

accumulation of massive numbers of organisms within the intestinal tract, and subsequent impaired nutrient absorption. However, patients with Whipple's disease do not appear to be prone to opportunistic infections or to malignancy.

CLINICAL MANIFESTATIONS

Spectrum of disease — The spectrum of clinical findings due to *T. whipplei* infection is wide.

Classic Whipple's disease is a multisystemic process characterized by joint symptoms, chronic diarrhea, malabsorption, and weight loss; many other organ systems can also be affected. The disease presents over time, with joint symptoms preceding the others by many years, so not all symptoms may be manifest at the time of presentation in affected individuals. Isolated involvement of other organs, most prominently the central nervous system (CNS) and heart valves, can also occur in the absence of the classic findings of Whipple's disease. In one report of 52 patients, for example, the frequency of abnormalities before diagnosis was: articular (67 percent); gastrointestinal (15 percent); systemic (14 percent); and CNS (4 percent) [44]. Articular symptoms preceded the diagnosis of Whipple's disease by a mean of six years.

There have also been reports of Whipple's disease being unmasked or accelerated by immunosuppressive therapy, typically given for presumed rheumatic disease, in some cases with severe complications, such as sepsis or disseminated *T. whipplei* infection [45].

Additionally, as molecular testing has facilitated the identification of the organism, more recent reports have associated *T. whipplei* with other syndromes. In a study of 241 children aged two to four years with acute gastroenteritis, *T. whipplei* was identified in 15 percent of cases (compared with none of the 47 controls); one-third were coinfected with other diarrhea pathogens [46]. *T. whipplei* has also been associated with nonspecific febrile illness in rural West Africa [47,48]. In a study of 204 Senegalese patients with fever and negative malaria tests, *T. whipplei* bacteremia, as detected by PCR of the blood, was observed in 13 cases (6.4 percent). Most affected individuals were children; associated clinical symptoms included cough and sleep disturbances.

Asymptomatic carriage of *T. whipplei* has also been described, with detection of *T. whipplei* DNA in stool and saliva specimens from healthy individuals [15-20]. The prevalence depends on the geographic area. In Europe, the prevalence of the bacterium in fecal samples from the healthy adult population is estimated to be 1 to 11 percent [21]. In a study among 465 inhabitants of a rural community in Gabon, the prevalence of *T. whipplei* DNA in stool samples was 20 percent, with higher prevalence among children [49].

Classic Whipple's disease — There are four cardinal clinical manifestations of late onset Whipple's disease [44]:

- Arthralgias
- Weight loss
- Diarrhea
- Abdominal pain

Additionally, various other findings have been reported in patients ultimately diagnosed with Whipple's disease. These are discussed in detail below.

Joint symptoms — Joint symptoms are common, reported in up to 80 percent of patients [50-53]. These typically present as migratory arthralgias of the large joints, but there is no clearly characteristic presentation, and these can also manifest as a chronic, migratory oligoarthritis or polyarthritis. Fixed joint involvement with effusion occurs uncommonly. Joint destruction or deformities are rare. Peripheral joints are most commonly affected (knees, wrists, and ankles). Myalgias often accompany the joint symptoms.

Many individuals who are ultimately diagnosed with classic Whipple's disease were initially misdiagnosed as having seronegative inflammatory arthritis. In one case series that included 113 patients with documented Whipple's disease, 50 percent had previously undergone immunomodulatory therapy, including anti-TNF alfa inhibitor treatment [50]. Thus, seronegative rheumatoid arthritis that does not improve with therapy should raise suspicion for Whipple's disease. (See 'Clinical suspicion' below.)

Certain features may be more common with Whipple's disease than with other causes of arthritis. In a questionnaire-based study of patients with Whipple's disease and certain rheumatologic conditions associated with joint symptoms, a presentation in males with episodic attacks that lasted about a week, sometimes involved the same joints, and spared the toes and to a lesser degree the distal finger joints was more strongly associated with Whipple's disease than with rheumatoid arthritis, psoriatic arthritis, or axial spondyloarthritis [54]. Episodic attacks were also common with palindromic rheumatoid arthritis but were more likely to be of acute onset, had a more conspicuous migratory character, and were less likely to affect the same joint compared with Whipple's disease.

GI symptoms and weight loss — Gastrointestinal symptoms generally occur later in the course of disease, after initial joint symptoms [51-53]. The main gastrointestinal manifestations are intermittent diarrhea with colicky abdominal pain. Watery diarrhea and steatorrhea have both been described, as have occult and gross gastrointestinal bleeding. This ultimately

progresses to a severe wasting syndrome and weight loss. Late findings include abdominal distention due to ascites associated with chronic malabsorption.

Additional features

- **Systemic** – Many patients with Whipple's disease do not report fever; it has been reported in approximately 25 to 40 percent [51,53]. Lymphadenopathy, predominantly of the mesenteric and mediastinal nodes, has been reported in up to half of cases [50]; in occasional cases, this can raise suspicion for lymphoma.

- **Neurologic** – Dementia and other central nervous system findings (such as supranuclear ophthalmoplegia, nystagmus, and myoclonus) occur more frequently in the later stages of the disease. These are discussed in further detail elsewhere. (See 'CNS disease' below.)

- **Cardiac** – In addition to endocarditis, *T. whipplei* infection has also been associated with pericarditis and myocarditis. (See 'Endocarditis' below.)

- **Dermatologic** – Skin hyperpigmentation can occur, reported in 40 to 45 percent [51,52]. The pathogenic mechanisms underlying this are uncertain but may be related to vitamin malabsorption [55].

- **Pulmonary** – Symptoms or signs related to pleuropulmonary disease, including pleural effusion, chronic cough, interstitial-lung disease-like presentation, and pulmonary hypertension, have also been reported in or attributed to Whipple's disease [56-59]. In one study of 42 patients, pleuropulmonary symptoms were reported in 13 percent [44].

- **Laboratory findings** – Laboratory abnormalities associated with chronic inflammation and malabsorption are common in patients with Whipple's disease. In a study that included 108 individuals with documented Whipple's disease, anemia was reported in 81 percent, and elevated leukocyte and platelet counts in 48 and 56 percent, respectively [53]. C-reactive protein was elevated in 69 percent. Other laboratory abnormalities include hypoalbuminemia and vitamin deficiency, including elevated prothrombin times secondary to vitamin K deficiency.

Other reported findings include ocular involvement (including uveitis and chorioretinitis) [60,61], prosthetic joint infection [62], and adrenal gland insufficiency [63].

CNS disease — Neurologic involvement can occur in the setting of classic Whipple's disease or as a manifestation of relapse after treatment. Neurologic findings have been reported in 10 to 40 percent of patients with classic Whipple's disease. Isolated CNS infection with *T. whipplei* can rarely occur. The incidence of CNS disease increases over time in an infected patient [30].

Most commonly, CNS involvement is asymptomatic and only diagnosed by PCR detection of *T. whipplei* in the CSF. Among patients with symptomatic CNS involvement, cognitive dysfunction, including dementia, other memory impairment, and confusion, is the most common abnormality [64]. Two findings, at least one of which is present in approximately 20 percent of such patients, are considered pathognomonic for Whipple's disease: oculomasticatory myorhythmia (continuous rhythmic movements of eye convergence with concurrent contractions of the masticatory muscles) and oculo-facial-skeletal myorhythmia [44,64,65]. These abnormalities are almost always accompanied by supranuclear vertical gaze palsy. (See "Pendular nystagmus", section on 'Oculomasticatory myorhythmia'.)

Cerebellar ataxia may be a more common feature of CNS disease than previously reported; in a retrospective review of 11 patients, cerebellar ataxia was present in five [66]. A variety of other neurologic findings have been described in case series, including myoclonus, hemiparesis, peripheral neuropathy, seizures, and upper motor neuron disorders [67]. Infection with *T. whipplei* may induce hypothalamic dysfunction. In patients with CNS symptoms, computed tomography (CT) or magnetic resonance imaging (MRI) of the brain may reveal nonspecific focal lesions that generally resolve with therapy [44].

Isolated neurologic involvement is rare and difficult to recognize. In one review of the literature that identified 20 patients with primary Whipple's disease of the brain, two clinical syndromes were identified [68]:

- Multifarious neurological symptoms and signs (eg, generalized seizures, ataxia, eye movement disorders, amnesic syndrome, syndrome of inappropriate anti-diuretic hormone secretion [SIADH], obstructive sleep apnea, insomnia, meningoencephalitis, hemiplegia, dementia, and others) with multiple enhancing lesions on CT or MRI (13 of 18 evaluable cases, 72 percent).

- Focal neurologic symptoms secondary to a solitary mass lesion (5 of 18 evaluable cases, 28 percent).

CSF investigation in patients with clinical CNS *T. whipplei* involvement is important. Usually, the CSF analysis is normal in asymptomatic patients. Patients with symptomatic CNS infection have a low to moderate pleocytosis (5 to 100 cells/microL) mostly made up of lymphocytes and monocytes or macrophages. Occasionally, periodic acid-Schiff (PAS)-positive macrophages can be identified in cytologic analysis of CSF. In addition, protein levels may be elevated and oligo-clonal bands may be present. In untreated patients, the CSF PCR for *T. whipplei* is positive when there is CNS involvement.

CNS manifestations have been associated with poor prognosis, including death, in some patients, even despite adequate therapy.

Endocarditis — Whipple endocarditis has been described in a small number of patients [8,44,69-72]. However, *T. whipplei* may be a more frequent cause of endocarditis than previously recognized. In a study of 255 patients whose explanted heart valves were positive for bacterial 16S rRNA gene amplification, *T. whipplei* was detected in 16 (6.3 percent) and was the most common cause of culture-negative endocarditis [73].

Endocarditis caused by *T. whipplei* may not be associated with the classical clinical presentation of Whipple's disease. Affected patients may have no clinical or histologic evidence of gastrointestinal disease or arthralgias [70-74].

In most cases, the diagnosis has been made by examination of the resected valve tissue [72]. The pathologic features include significant fibrosis, slight inflammation with foamy macrophages, lack of calcifications, and vegetations of intermediate size [72]. The prominent fibrosis with only slight inflammation suggests a slowly progressive infection, similar to that seen in Q fever and bartonellosis, which are other causes of culture-negative endocarditis [75]. *T. whipplei* can be detected in the resected valve by immunohistochemical analysis, which correlates with detection by culture or polymerase chain reaction.

DIAGNOSIS

Clinical suspicion — Although Whipple's disease has a reputation as a great mimicker of many different illnesses, the difficulty in diagnosis is probably more a function of its rarity than its stealth. It should be considered in all patients with the four cardinal manifestations (arthralgias, diarrhea, abdominal pain, and weight loss) after more common conditions have been excluded (algorithm 1). Suspicion of the diagnosis is more difficult in those patients (15 percent in one series) who do not develop gastrointestinal symptoms [44]. In particular, it should be a consideration in patients with rheumatoid factor-negative migratory polyarthritis that does not respond to immunosuppressive therapy. (See 'Joint symptoms' above.)

Other clinical syndromes that suggest the possible diagnosis of Whipple's disease include fever of unknown origin, chronic serositis, progressive central nervous system disease or early onset cognitive deficits with myoclonus or ophthalmoplegia, and generalized lymphadenopathy. Accompanying vitamin or iron deficiency anemia, hypoalbuminemia, and relative lymphopenia should increase the level of suspicion.

Evaluation — Because Whipple's disease is rare compared to other systemic illnesses that may present with similar signs and symptoms, the first step in the evaluation of Whipple's disease is to assess for alternative, more common diagnoses. Often Whipple's disease is not suspected until after such diagnoses have been ruled out (algorithm 1). (See 'Ruling out alternate diagnoses' below.)

Once this is done, the approach depends on the clinical presentation:

- For patients with suspected Whipple's disease who have gastrointestinal symptoms, we start with upper endoscopy with biopsies of the small intestine for *T. whipplei* testing (histology with periodic acid-Schiff [PAS] staining, polymerase chain reaction [PCR] testing, and immunohistochemistry). If results from small bowel biopsy testing are indeterminate, we obtain specimens from other sites of involvement (eg, synovial fluid, lymph nodes, cerebrospinal fluid [CSF]) for *T. whipplei* testing. (See 'Testing of small bowel biopsy' below.)

- For patients with suspected Whipple's disease who do not have gastrointestinal symptoms, specimens for *T. whipplei* testing are typically first taken from the relevant anatomical site (eg, synovial fluid or tissue from patients with arthralgias, CSF from patients with a neurologic presentation, lymph nodes from a patient with lymphadenopathy). For patients with endocarditis, *T. whipplei* testing is performed on the resected valve. PCR of noninvasive specimens (urine, stool, or saliva) lacks sensitivity for diagnosis of localized Whipple's disease (non-classical); thus these invasive samples should be tested on the basis of clinical manifestations. If testing of these invasive specimens is negative but no alternate diagnosis has been established and Whipple's disease remains in the differential diagnosis, we perform endoscopy with small bowel biopsy since it is a simple and safe diagnostic test. Even if testing of these specimens is positive for *T. whipplei*, we still pursue endoscopy and small bowel biopsy for *T. whipplei* testing to increase support for the diagnosis given that asymptomatic gut involvement is common even with extraintestinal presentations of Whipple's Disease.

Generally, the diagnosis of Whipple's disease can be made with PAS-positive staining on a small bowel biopsy or when two *T. whipplei* tests from gastrointestinal and/or extraintestinal specimens are positive. (See 'Diagnostic criteria' below.)

All patients with a diagnosis of Whipple's disease also undergo lumbar puncture for PCR testing of the CSF to evaluate for central nervous system involvement, if this has not already been done. (See 'Evaluation for CNS involvement' below.)

The individual steps in the evaluation for Whipple's disease are discussed in further detail below.

Ruling out alternate diagnoses — Given the relative rarity of Whipple's disease, other more common disorders that cause diarrhea, arthralgias, or central nervous system (CNS) symptoms should be ruled out first. The differential diagnosis is wide and depends on the presentation. Potential etiologies and evaluation of such symptoms are discussed in detail elsewhere:

- (See "Approach to the adult with chronic diarrhea in resource-abundant settings".)
- (See "Evaluation of the adult with polyarticular pain".)
- (See "Early-onset dementia in adults".)

In particular, among the disorders which should be excluded prior to making a diagnosis of Whipple's disease are:

- Inflammatory bowel disease with migratory polyarthropathy (see "Endoscopic diagnosis of inflammatory bowel disease in adults")
- Infectious causes of chronic diarrhea (see "Approach to the adult with chronic diarrhea in resource-abundant settings", section on 'Chronic infections')
- Connective tissue disease (see "Undifferentiated systemic rheumatic (connective tissue) diseases and overlap syndromes", section on 'General approach to the patient')
- Hyperthyroidism (see "Diagnosis of hyperthyroidism")
- HIV infection (see "Screening and diagnostic testing for HIV infection")
- Tuberculosis (see "Clinical manifestations, diagnosis, and treatment of miliary tuberculosis")

Testing of small bowel biopsy — Upper gastrointestinal endoscopy with biopsies of the small intestine is the diagnostic test of choice (algorithm 1) [44,65]. It is generally the first test performed for the evaluation of Whipple's disease in patients with gastrointestinal symptoms, but it is also performed in patients with suspected extraintestinal Whipple's disease to clarify or confirm the diagnosis.

A prothrombin time should be checked prior to biopsy because of the frequent occurrence of vitamin K malabsorption. To improve the yield, we generally take 7 to 10 biopsies from different parts of the duodenum. The biopsy specimens should be submitted for PAS staining and PCR testing. Clinical pathology laboratories can perform PAS staining, and PCR testing is available through commercial laboratories. If these are unrevealing and the suspicion remains high, immunohistochemistry can be performed, but this test is generally available only through a reference center.

Biopsy specimens should be obtained when Whipple's disease is suspected even if there are no gross small bowel abnormalities, as many patients with Whipple's disease have normal appearing mucosa. In one study of 191 patient with Whipple's disease, only 26 percent had an

abnormal appearing duodenum; 11 percent had findings that have been considered characteristic for Whipple's disease (ie, dilated villi, ectatic lymph vessels, prominent or discrete edema) and 10 percent had evidence of duodenitis [53].

Whipple's disease is characterized by PAS-positive macrophages on small bowel biopsy, which is usually readily apparent and unlikely to be confused with other diseases (see 'Differential diagnosis' below). The main histologic features are extensive PAS-positive material in the lamina propria [2,76] and villous atrophy (picture 1).

Results of PCR testing can also be used to make the diagnosis; the amplified DNA should be sequenced. In one series of 30 specimens from patients with histologically confirmed Whipple's disease, the sensitivity and specificity of PCR were 97 and 100 percent, respectively [77]. Lower specificity was found in another study that estimated the test to be 95 percent specific when performed on a duodenal biopsy, and 87 percent specific when performed on gastric juice [15]. False positive tests might result from the presence of *T. whipplei* or a closely related bacterium, which may be present in a substantial proportion of the population in the absence of Whipple's disease. Positive tests may also represent asymptomatic *T. whipplei* colonization.

Testing of other specimens — If small bowel biopsies are nondiagnostic but the suspicion for Whipple's disease remains or if the patient initially presents with extraintestinal symptoms, other tissue or fluid specimens can be obtained for *T. whipplei* testing (PAS staining, PCR testing, and if available, immunohistochemistry) (algorithm 1).

PAS staining and, if available, immunohistochemistry can be performed on tissue or cells that have been collected through centrifugation of a fluid specimen. PCR testing can be used to identify *T. whipplei* in fresh or formalin-fixed intestinal and lymphatic tissue [5], vitreous fluid in Whipple's uveitis [60], peripheral blood, cardiac valves [72,78], cerebrospinal fluid (CSF) [79], and synovial fluid and tissue [80,81]. PCR can also detect *T. whipplei* in urine specimens in patients with untreated classic Whipple's disease, but it may be less sensitive in patients with localized infection [82].

Other tests have minimal role in the diagnosis of Whipple's disease. Some laboratories perform *T. whipplei* PCR on blood specimens, although the clinical utility of this test has not yet been defined [83,84]. Development of an immunofluorescence assay using the cultured organism has been pursued, although cross-reactivity might make clinical use of this tool difficult [7,8]. Use of western blot serology has been described to distinguish between asymptomatic carriers and patients with clinical disease, but this is not used clinically as part of the diagnostic workup [85].

Evaluation for CNS involvement — Since neurologic manifestations of Whipple's disease have the most disabling consequences, PCR for *T. whipplei* DNA should be performed on CSF

when the possibility of Whipple's disease is being entertained as a cause of neurological symptoms. *T. whipplei* PCR should also be performed on the CSF whenever Whipple's disease is diagnosed, even if there are no neurological symptoms [53]. Many neurologically asymptomatic patients with Whipple's disease have *T. whipplei* DNA detected on CSF PCR. As an example, in one study, 7 of 10 (70 percent) Whipple's disease patients without neurological symptoms had a positive CSF *T. whipplei* PCR, compared with 4 of 5 (80 percent) with neurologic symptoms [86].

The observation that PCR of the cerebrospinal fluid is often positive in patients without neurologic symptoms suggests that late CNS symptoms probably reflect progression of initially occult infection [86].

Diagnostic criteria — The diagnosis of Whipple's disease can be made with the classic finding of PAS-positive macrophages from a small bowel biopsy (algorithm 1). In the absence of this finding, the diagnosis can also be made when two different *T. whipplei* tests (PAS, PCR, or immunohistochemistry) from the same specimen or two *T. whipplei* tests from different specimens are positive (eg, with positive PAS staining and PCR from a synovial specimen or with positive PCR from both a small bowel biopsy and a synovial specimen).

If only one *T. whipplei* test is positive, Whipple's disease is possible, but the diagnosis remains uncertain. Additional testing (eg, performance of staining for mycobacteria on PAS-positive specimens) or repeating *T. whipplei* testing on the positive or other relevant specimens can help clarify the diagnosis over time.

The diagnosis of *T. whipplei* endocarditis is generally made by positive *T. whipplei* testing of a resected heart valve, usually by histology and/or immunohistochemistry. *T. whipplei* PCR often becomes negative soon after initiation of antibiotic therapy, which most individuals with endocarditis receive prior to valve explant.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for the various signs and symptoms associated with Whipple's disease is broad, but because of its rarity, Whipple's disease is generally considered only after the more common causes have been ruled out. (See 'Ruling out alternate diagnoses' above.)

Histologically, there are few other conditions that have a similar appearance (ie, periodic acid-Schiff positivity) on small bowel biopsy. Other infections, such as with endemic fungi (eg, *Histoplasma* spp), *Rhodococcus*, and HIV-infected mycobacterial disease, can be histologically similar to Whipple's disease, but many can be ruled in or out by additional testing (ie, staining for organisms, culture, antigen testing).

TREATMENT

Antimicrobial resistance — In vitro susceptibility testing of *T. whipplei* to antibiotics in cell culture using a real-time PCR assay has demonstrated that doxycycline, macrolides, ketolides, aminoglycosides, penicillin, rifampin, teicoplanin, chloramphenicol, and trimethoprim-sulfamethoxazole (TMP-SMX) have activity, with MICs ranging from 0.25 to 2 mcg/mL [87-89]. A combination of doxycycline and hydroxychloroquine was bactericidal [88].

Fluoroquinolones are not active against *T. whipplei*. Sequence analysis of the gyrA and parC genes identified amino acid substitutions associated with increased fluoroquinolone resistance in *Escherichia coli*; these amino acid substitutions are thus likely responsible for intrinsic fluoroquinolone resistance in *T. whipplei* [87].

In addition, *T. whipplei* does not contain the gene that encodes dihydrofolate reductase, the target for trimethoprim activity; thus the activity of TMP-SMX is due to sulfamethoxazole alone [89].

Initial management — Whipple's disease was uniformly fatal prior to the availability of antibiotics but can be successfully treated with them.

Our preferred regimen — The optimal regimen is uncertain. For patients with chronic Whipple's disease (either classic or localized chronic infection), we suggest an initial phase of an intravenous antibiotic that is active against *T. whipplei* and is known to penetrate the blood-brain barrier, followed by 12 months of oral maintenance therapy with trimethoprim-sulfamethoxazole (TMP-SMX) (table 1). The dose and duration of intravenous therapy and the need for adjunctive therapy depends on the clinical presentation:

- **Classic Whipple's** – For patients with Whipple's disease without evidence of CNS involvement, we suggest initial therapy with ceftriaxone (2 g IV once daily) or penicillin (2 MU IV every 4 hours) for two weeks, followed by TMP-SMX (one double-strength tablet [160 mg TMP/800 mg SMX] twice a day) for one year [90].

- **Central nervous system disease** – For patients with CNS disease (including those with asymptomatic positive PCR testing in the CSF), we suggest ceftriaxone (2 g IV once daily) or penicillin G (4 MU IV every 4 hours) for two weeks, followed by TMP-SMX (one double-strength tablet [160 mg TMP/800 mg SMX] twice a day) for one year. Some clinicians extend parenteral treatment to four weeks for CNS disease, although there is no clear evidence that this improves outcomes. Although the dosing of ceftriaxone for other CNS

infections is generally 2 g IV every 12 hours, observational studies have suggested that 2 g IV once daily is adequate for Whipple's disease.

CNS involvement continues to be very difficult to manage. For those who have severe CNS symptoms or brain lesions, adjunctive corticosteroids may be beneficial, as is given for tuberculous meningitis. (See "Central nervous system tuberculosis: Treatment and prognosis".)

- **Endocarditis** – For patients with endocarditis, we suggest penicillin G (2 MU IV every 4 hours) or ceftriaxone (2 g IV once daily) for four weeks, followed by TMP-SMX (one double-strength tablet [160 mg TMP/800 mg SMX] twice a day) for one year. Surgical resection of the infected valve is typically already performed as the diagnosis can only be made from testing the explanted valve.

The rationale for our preferred regimen is that adequate CNS activity may be critical to preventing relapse; relapse often manifests with evidence of CNS infection or involvement, thought to reflect an initial and potentially subclinical CNS infection that was not adequately treated. Given the rarity of the disease, treatment efficacy studies are difficult, and the evidence to support this regimen is primarily observational. In a prospective trial of 40 European patients with Whipple's disease randomly assigned to induction therapy with ceftriaxone versus meropenem for 14 days, each followed by oral TMP-SMX, all patients achieved clinical and histologic cure at one year [91]. All except one remained in remission after a mean follow-up of three years. That one patient had asymptomatic detection of *T. whipplei* DNA in the CSF by PCR despite sequential treatment with both regimens. Other case reports and retrospective studies have also documented good outcomes without relapse with a regimen of an intravenous beta-lactam followed by prolonged TMP-SMX therapy [44,92]. The rationale for prolonged therapy is to permit complete eradication of the organism, thereby reducing the likelihood of relapse. With intravenous induction therapy, an abbreviated TMP-SMX course may also be effective. This was suggested by a prospective study of 40 patients treated with intravenous ceftriaxone for two weeks followed by three months of TMP-SMX; only one patient had symptomatic relapse after a mean follow-up of 80 months [93]. However, we do not routinely recommend an abbreviated course of treatment at this time.

A proposed alternative to this regimen has been doxycycline plus hydroxychloroquine (the combination of which has been demonstrated to be bactericidal in vitro) with the addition of a sulfa agent for those with CNS involvement. One retrospective study from France reported no treatment failures in 13 patients who received the combination of doxycycline plus hydroxychloroquine (with or without a sulfa agent), in contrast to a high failure rate (including on-treatment failure and relapse) with TMP-SMX, even if induction intravenous therapy was

given [94]. The reasons for such discrepancies compared with other studies, which mainly included patients from Germany and Austria, are unclear and have been hypothesized to be related to possible host factors or bacterial strains specific to the different regions. A randomized trial is underway to compare these regimens (an intravenous induction followed by TMP-SMX versus doxycycline plus hydroxychloroquine).

Tetracycline alone had previously been the mainstay of therapy until a comprehensive review demonstrated a relapse rate of 35 percent among patients treated primarily with that agent [95]. TMP-SMX appeared more effective than tetracycline in inducing remission (92 versus 59 percent, respectively, in a retrospective study of 30 patients [96]). However, relapses were also reported with TMP-SMX, in some cases while the patients were still taking the drug [92,97]. This resulted in the suggestion that initial therapy should include an intravenous agent that attains adequate CSF levels.

Beta-lactam or sulfa allergy

- Ceftriaxone and penicillin allergy — For patients who cannot use ceftriaxone or penicillin, meropenem (1 g every eight hours) for two to four weeks (depending on the extent of disease) is an alternative for the initial intravenous phase. This is followed by TMP-SMX (one double-strength tablet [160 mg TMP/800 mg SMX] twice a day) for one year. The use of carbapenems in individuals with beta-lactam allergies is discussed elsewhere. (See "Allergy evaluation for immediate penicillin allergy: Skin test-based diagnostic strategies and cross-reactivity with other beta-lactam antibiotics", section on 'Recommended approach' and "Immediate cephalosporin hypersensitivity: Allergy evaluation, skin testing, and cross-reactivity with other beta-lactam antibiotics", section on 'Carbapenems and monobactams'.)

- Sulfa allergy — Following the intravenous induction with ceftriaxone or penicillin, an alternative regimen for maintenance therapy is doxycycline (100 mg PO twice daily) in combination with hydroxychloroquine (200 mg PO thrice daily) [88].

Evaluation of clinical response — Most adequately treated patients do well. Clinical improvement is often dramatic, occurring within 7 to 21 days [44]. However, neurological symptoms are occasionally irreversible.

The response to treatment can be monitored by following the patient's hematocrit, weight, and symptom resolution. There are no clear data to guide repeat *T. whipplei* testing as a way to monitor response. We often repeat small bowel biopsy each year for the first five years, then every three to five years unless new symptoms prompt an earlier evaluation. PCR testing of small bowel biopsy may have some predictive value for future relapse; in one series of small

bowel biopsies obtained after successful initial therapy, relapse occurred in none of 5 patients who were PCR-negative compared to 7 of 12 who were PCR-positive [77]. For patients with an initial positive PCR in the CSF, we repeat CSF PCR every two to three months until it is negative; subsequently, we only check CSF PCR if new or recurrent neurologic findings occur. Alternatively, it is reasonable to only repeat *T. whipplei* testing if symptoms do not resolve or concerning new symptoms arise.

There have been several reported cases of Jarisch-Herxheimer reactions one to two hours after initial therapy of Whipple's disease with intravenous antibiotics, especially penicillin. The reaction consists of fever of 39º to 40ºC, chills, headache, hypotension, and severe abdominal pain or pleuritic chest pain [22].

Other issues to monitor for are immune reconstitution inflammatory syndrome (IRIS) and treatment failure or relapsing infection after initial remission, discussed below.

IRIS — In the first few weeks following initiation of antibiotic treatment, some patients who have received appropriate therapy may develop an immune reconstitution inflammatory syndrome (IRIS) with high fever or other symptoms that mimic relapse or disease progression [51,98]. In contrast to disease relapse, PCR testing of the relevant specimen is often negative. IRIS reflects an inflammatory process that occurs despite successful therapy of the organism. Those at risk for developing IRIS after starting therapy for Whipple's disease include:

- Patients who have been treated with immunosuppressive therapy for presumed rheumatic disease for an extended period prior to the diagnosis of Whipple's disease, whose immunosuppressive therapy is discontinued at the start of antibiotic treatment.
- Patients with CNS involvement of Whipple's disease.

In these circumstances, corticosteroid therapy may be beneficial; further study is needed.

Relapse — Clinical failure is suggested by a positive PCR in the relevant specimen from patients who fail to respond clinically to adequate therapy or have recurrence of symptoms after initial improvement. Clinical relapses have been reported in as many as 17 to 35 percent of patients [44,99] and, as noted above, in 7 of 12 patients who remained PCR-positive on small bowel biopsy obtained after initial therapy [77]. However, many patients with suspected relapse in these studies may have actually had IRIS. It is assumed that relapses reflect incomplete eradication of the organism with initial therapy.

For patients who fail to respond to initial therapy or relapse, we suggest penicillin G (4 MU IV every 4 hours) or ceftriaxone (2 g IV twice daily) for four weeks **followed by** oral doxycycline

(100 mg twice daily) in combination with hydroxychloroquine (200 mg PO thrice daily) [87] **OR** TMP-SMX (one double-strength tablet [160 mg TMP/800 mg SMX] twice a day) for one year (table 1). If a CNS relapse occurs after a lower dose of ceftriaxone, a higher dose (2 g IV twice daily) may be more effective [92]. Occasional patients have required chronic intravenous ceftriaxone therapy for control of CNS symptoms [65].

SUMMARY AND RECOMMENDATIONS

- **Causative organism** – Whipple's disease is caused by *Tropheryma whipplei*, a gram-positive, non-acid-fast, periodic acid-Schiff (PAS)-positive rod. The organism is ubiquitous in the environment but only rarely causes chronic disease. (See 'Microbiology' above and 'Epidemiology' above.)

- **Classic features** – Classic Whipple's disease is a multisystemic process that presents over time, and is described most commonly occurs in White males of European ancestry. Joint symptoms, typically migratory arthralgias of the large joints, generally precede other manifestations by many years. Later in the course of disease, intermittent diarrhea with colicky abdominal pain occur and ultimately can progress to a severe wasting syndrome. (See 'Classic Whipple's disease' above.)

- **Neurologic and cardiac involvement** – Many other organ systems can also be affected, including the central nervous system (CNS). With earlier diagnosis, asymptomatic CNS involvement is most common, although cognitive dysfunction, including dementia, other memory impairment, and confusion, is also common with CNS involvement. Isolated involvement of certain organs, most prominently the CNS and heart valves, can also occur in the absence of the classic findings of Whipple's disease. (See 'Spectrum of disease' above and 'CNS disease' above and 'Endocarditis' above.)

- **Clinical suspicion** – Whipple's disease should be considered in all patients with the four cardinal manifestations (arthralgias, diarrhea, abdominal pain, and weight loss). Suspicion of the diagnosis is more difficult in those patients who do not develop gastrointestinal symptoms. In particular, it should be a consideration in patients with rheumatoid factor-negative migratory polyarthritis that does not respond to immunosuppressive therapy. (See 'Clinical suspicion' above.)

- **Rule out alternate diagnoses** – Because Whipple's disease is rare compared with other systemic illnesses, the first step in the evaluation of Whipple's disease is to assess for alternative, more common disorders that cause chronic diarrhea, arthralgias, or

progressive CNS disease. The differential diagnosis is wide and depends on the presentation; in particular, it includes inflammatory bowel disease, infectious causes of chronic diarrhea, connective tissue disease, hyperthyroidism, and HIV infection. (See 'Ruling out alternate diagnoses' above and "Approach to the adult with chronic diarrhea in resource-abundant settings" and "Evaluation of the adult with polyarticular pain" and "Early-onset dementia in adults".)

- **Diagnostic evaluation** – For patients with gastrointestinal symptoms and suspected Whipple's disease, we perform upper endoscopy and biopsies of the small intestine for *T. whipplei* testing. If these results are indeterminate, we obtain specimens from other sites of involvement (eg, synovial fluid, lymph nodes, cerebrospinal fluid [CSF]) for *T. whipplei* testing. For patients with suspected Whipple's disease who do not have gastrointestinal symptoms, specimens are typically first taken from the relevant anatomical site, but small bowel biopsy is still pursued to increase support for the diagnosis. *T. whipplei* testing includes histology with PAS staining, polymerase chain reaction (PCR) testing, and immunohistochemistry (algorithm 1). (See 'Evaluation' above and 'Testing of small bowel biopsy' above and 'Testing of other specimens' above.)

- **Diagnostic criteria** – The diagnosis of Whipple's disease can be made with the classic finding of PAS-positive macrophages from a small bowel biopsy. In the absence of this finding, the diagnosis can also be made when two different *T. whipplei* tests from the same specimen or two *T. whipplei* tests from different specimens are positive. For all patients diagnosed with Whipple's disease, *T. whipplei* PCR should be performed on the CSF, even if there are no neurological symptoms. (See 'Diagnostic criteria' above and 'Evaluation for CNS involvement' above.)

- **Antibiotic therapy** – Whipple's disease requires prolonged antibiotic therapy. The optimal regimen for Whipple's disease is uncertain. For patients with Whipple's disease (either classic or localized chronic infection), we suggest a regimen with an initial phase of an intravenous antibiotic that is active against *T. whipplei* and is known to penetrate the blood-brain barrier, such as penicillin or ceftriaxone, followed by maintenance therapy with oral trimethoprim-sulfamethoxazole (TMP-SMX) (**Grade 2C**). The dose and duration of intravenous therapy and the need for adjunctive therapy depend on the clinical presentation (table 1). TMP-SMX maintenance therapy is given for 12 months. An alternative regimen consists of doxycycline plus hydroxychloroquine with the addition of a sulfa agent for those with CNS involvement. (See 'Initial management' above and 'Our preferred regimen' above.)

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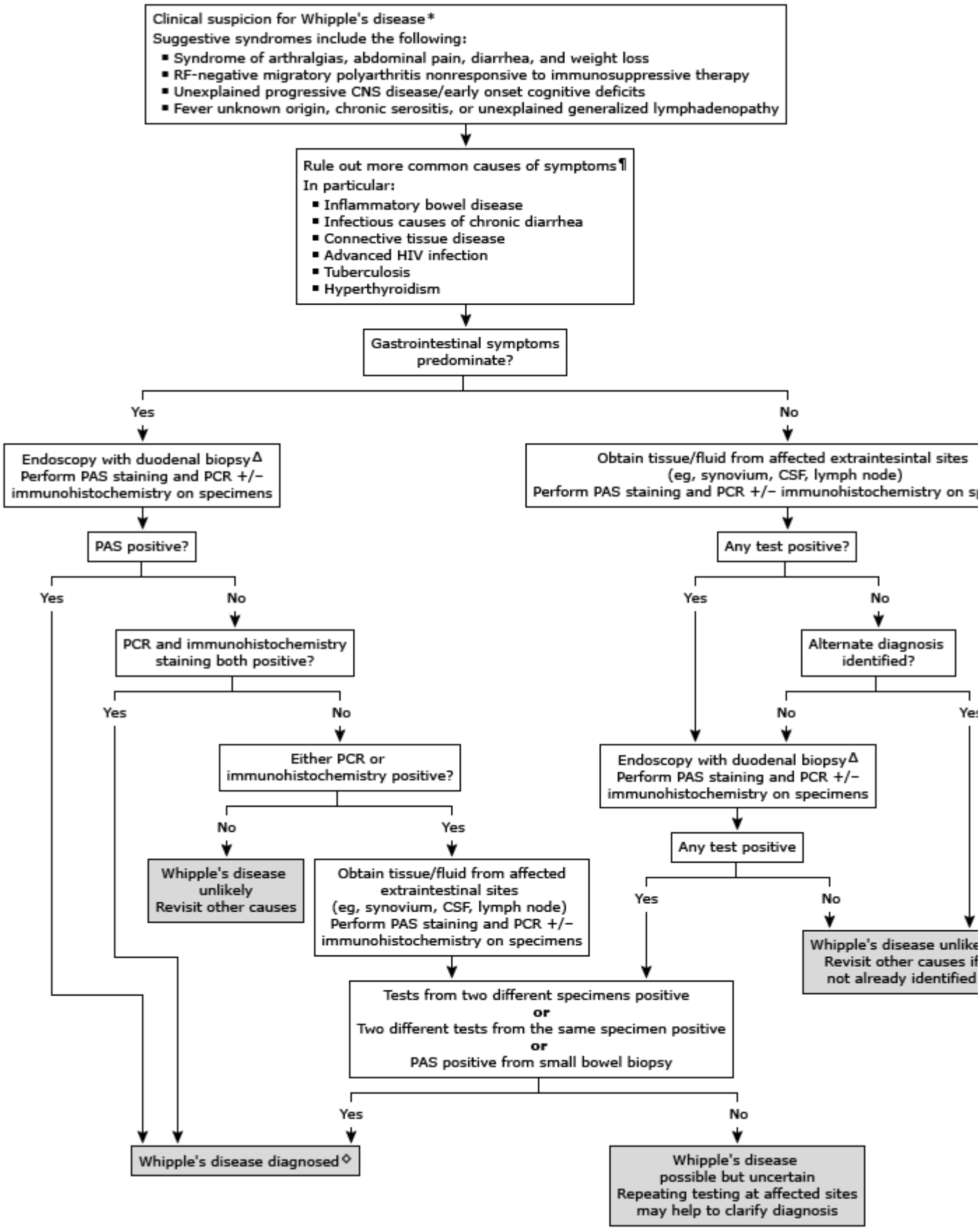
GRAPHICS

Approach to the diagnosis of Whipple's disease



CNS: central nervous system; CSF: cerebrospinal fluid; HIV: human immunodeficiency virus; PAS: periodic aci
Schiff; PCR: polymerase chain reaction.

* Classic Whipple's disease is a multisystemic process that presents over time. Joint symptoms, typically mig arthralgias of the large joints, generally precede other manifestations by many years. Later in the course of disease, intermittent diarrhea with colicky abdominal pain occur and ultimately progress to a severe wastinç syndrome. Many other organ systems can also be affected, including the central nervous system.

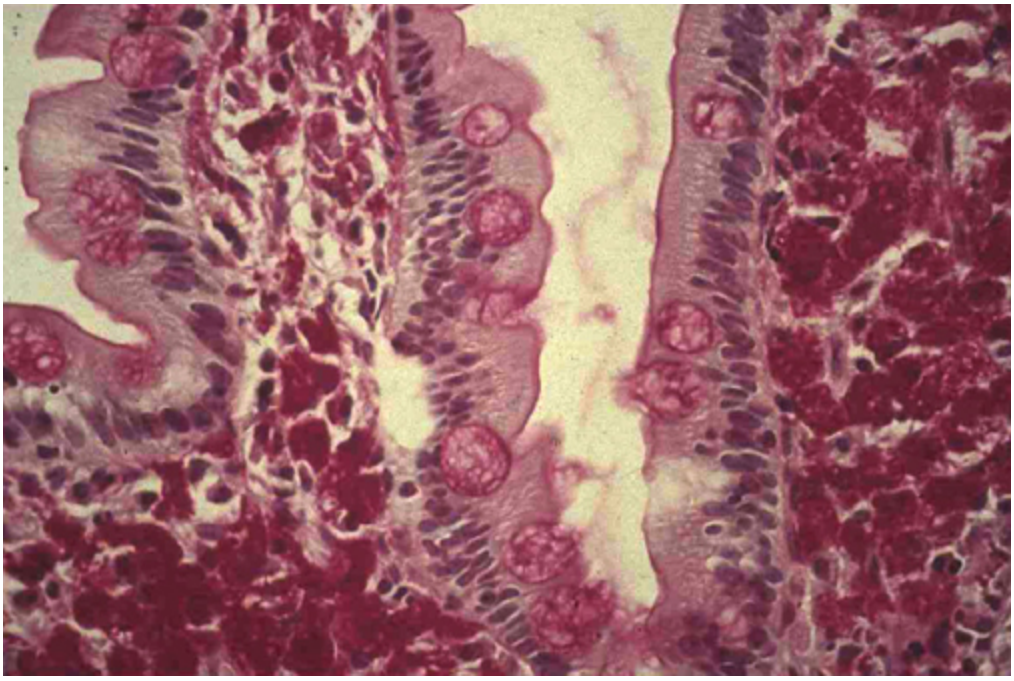
¶ The first step in the evaluation of Whipple's disease is to assess for alternative, more common disorders th cause chronic diarrhea, arthralgias, or progressive CNS disease. The differential diagnosis is wide and deper the presentation.

Δ Endoscopy with small bowel biopsy is a safe and simple diagnostic test that we perform whenever the pos of Whipple's disease is being considered, even in patients with predominantly extraintestinal features. We ty obtain seven to ten biopsies from different parts of the duodenum and, if possible, sample the stomach and proximal jejunum.

◇ CSF PCR, if not already performed, is checked on all patients diagnosed with Whipple's disease to evaluate CNS involvement.

Graphic 105131 Version 1.0

PAS positive macrophages on microscopy



PAS-positive macrophages in the small intestine of an untreated patient with Whipple's disease.

Graphic 61070 Version 2.0

Antimicrobial therapy in Whipple's disease

Indication	Agent	Duration
Initial therapy		
Initial phase*		
General infection	Ceftriaxone 2 g IV once daily **OR** Penicillin G 2 million units IV every four hours	Two weeks
Endocarditis	Penicillin G 2 million units IV every four hours **OR** Ceftriaxone 2 g IV once daily	Four weeks
Central nervous system disease¶	Ceftriaxone 2 g IV once daily **OR** Penicillin G 4 million units IV every four hours	Two to four weeks
If ceftriaxone and penicillin allergic	Meropenem 1 g IV every eight hours	Two to four weeks
Maintenance phase		
All infections	Trimethoprim-sulfamethoxazole one DS tablet twice daily	One year
If sulfa allergic	Doxycycline 100 mg PO twice daily **PLUS** Hydroxychloroquine 200 mg PO thrice daily	One year
Therapy for relapse		
Initial phase*	Penicillin G 4 million units IV every four hours **OR** Ceftriaxone 2 g IV twice daily	Four weeks
Maintenance phase	Doxycycline 100 mg PO twice daily **PLUS** hydroxychloroquine 200 mg PO thrice daily	One year

	OR Trimethoprim-sulfamethoxazole one DS tablet twice daily for one year	

IV: intravenously; IM: intramuscularly; DS: double-strength (one double-strength tablet is equivalent to 160 mg trimethoprim and 800 mg sulfamethoxazole); PO: orally.

* The initial phase is followed by the maintenance phase.

¶ Central nervous system disease includes neurologically asymptomatic patients with a positive cerebrospinal fluid (CSF) polymerase chain reaction (PCR) test for *Tropheryma whipplei* as well as patients with Whipple's disease and neurologic symptoms despite a negative CSF PCR test.

Graphic 65520 Version 5.0

Contributor Disclosures

Michael D Apstein, MD No relevant financial relationship(s) with ineligible companies to disclose. **Thomas Schneider, MD, PhD** Grant/Research/Clinical Trial Support: Deutsche Forschungsgemeinschaft (German State) [small intestinal infections]. All of the relevant financial relationships listed have been mitigated. **Stephen B Calderwood, MD** Consultant/Advisory Boards: Day Zero Diagnostics [Whole genome sequencing for microbial identification and determination of antimicrobial susceptibility]. All of the relevant financial relationships listed have been mitigated. **Allyson Bloom, MD** No relevant financial relationship(s) with ineligible companies to disclose.

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